## Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-131 are pending in this application and are rejected on various grounds. Claims 119-123 and 126-128 have been canceled without prejudice or disclaimer. Claim 124 has been amended for clarity to remove references to extracellular domains and signal sequences and with the functional recitation: "wherein, the nucleic acid encoding said polypeptide is amplified in squamous cell-type lung carcinomas or colon tumors." Claim 130 has been amended for proper claim dependency. The rejections to the presently pending claims are respectfully traversed.

## Specification

The disclosure was objected to by the Examiner for an informality which has been amended. Further, the foregoing amendments to the specification have deleted all embedded hyperlinks. Accordingly, Applicants believe that all objections to the specification have been overcome and should be withdrawn.

## Claim Rejections – 35 USC § 112, second paragraph

Claims 119-124, 127-128 are rejected under 35 U.S.C. §112, second paragraph for being indefinite.

In view of the cancellation of Claims 119-123 and 126-128, this rejection has been obviated with respect to these claims. Further, Applicants have deleted all references to "extracellular domain," "signal sequence" etc. in claim 124 for clarity. Accordingly, Applicants submit that the claims are definite and respectfully request that this rejection be withdrawn.

## Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 19-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility."

Claims 119-131 is further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

For the reasons outlined below, Applicants respectfully disagree.

**Utility Standard**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the

facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

**Arguments**

As discussed under the section on "priority", Applicants rely on the gene amplification data for patentable utility for the PRO290 protein.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 170 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9A (pages 550 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9A.

**A *prima facie* case of lack of utility has not been established**

The Examiner asserts, that "while the disclosed nucleic acid...has utility as a screening probe to detect squamous cell-type lung carcinomas, the polypeptide has no such utility", and relies on an exemplary literature report like Pennica and Haynes *et al.* for support and hence concludes that the PRO290 polypeptides lack utility.

According to the Examiner, Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, . . . . In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared

with expression in normal colonic mucosa from the same patient." (Emphasis added). Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

Further, the Examiner states that "Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold." Applicants respectfully further point out that, Haynes found that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there was a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation was "not linear" and hence, Haynes states that "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data showed that a positive correlation exists between mRNA and protein levels (although the correlation is not linear and hence, cannot be used to predict protein levels). Further, the Haynes data meets the "more likely than not standard" since it studies 80 proteins and shows "a general positive trend" in most proteins. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, is typical based on Pennica and Haynes. In fact,

contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Haynes *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

**It is "more likely than not" for amplified genes to have increased mRNA and protein levels**

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, just as in Haynes, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Ornoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Ornfoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO290 gene, that the PRO290 protein is

concomitantly overexpressed. Thus, Applicants submit that the PRO290 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

**Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence**

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or

over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO290 polypeptide, for example, in detecting over-expression or absence of expression of PRO290. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides of the instant invention, which concerns polypeptides having 100% sequence identity with the disclosed polypeptide sequence SEQ ID NO: 33 and further, with the functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in squamous cell-type lung carcinomas or colon tumors."

Thus, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

**Claim Rejections – 35 USC § 112, first paragraph- written description**

Claims 119-124, 126, 128 and 130 and 131 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner contends that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the pending claims.

**The Legal standard for Written Description**

The well- established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *In re* Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v.

Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. see e.g. Vas-Cath, Inc. v. Mahurkar, 935 F. 2d at 1563, 19 USPQ2d at 1116 (Fed. cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F. 3d 989, 996 (Fed. Cir. 2000).

**Arguments**

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The instant invention, defined by the claims, concerns polypeptides having 100% sequence identity with the disclosed polypeptide sequence SEQ ID NO: 33 and further, with the functional recitation: "wherein the nucleic acid encoding said polypeptide is amplified in squamous cell-type lung carcinomas or colon tumors." Based on the detailed description of the cloning and expression of variants of PRO290 in the specification, the description of the gene amplification assay and the actual reduction to practice of sequence SEQ ID NO: 33, the functional recitation in the instant claims, Applicants submit that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims.

Hence, Applicants submit that this rejection should be withdrawn.

## Priority

Applicants rely on the gene amplification assay for patentable utility of this case. This was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Hence, the instant application is at least entitled to an effective filing date of **June 23, 1999.**

## Claim Rejections - 35 USC § 102

Claims 119-123, 126, 128 are rejected under 35 U.S.C. §102(b) as being anticipated by GenBank AB011112.1 (dated 10 April 1998).

In view of the cancellation of claims 119-123, 126-128 this rejection is obviated for these claims; hence, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C3). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 20, 2004

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